REMARKS

Amendments to the Claims

Claim 5 has been cancelled without prejudice.

New claims 33-35 have been added, dependent or ultimately dependent on claim 1, specifying the nature of the repeats. Support is found, e.g., in the final paragraph of page 15 of the Specification.

New claims 36-39 have been added, dependent or ultimately dependent on claim 24. New claim 36 specifies that the organism is an insect, supported on page 16, line 37, and throughout the Specification. New Claims 37-39 specify the nature of the repeats, supported in the final paragraph of page 15 of the Specification.

Claim 27 has been made dependent on new claim 37.

No new matter has been added.

Claims 1-4, 6-13, and 19-39 are pending herein.

Allowable Subject Matter

The Examiner is thanked for identifying allowable subject matter. The Office Action states:

> Claims 2-5, 7, 9, 11-13, 21 and 27-31 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

The suggestion for amendment has not been adopted, as it is believed the arguments presented below render the claims allowable without amendment.

The Anticipation Rejection

Claims 1, 6, 8, 10,19, 20, 22-26 and 32 have been rejected under 35 U.S.C. 102(b) as allegedly anticipated by Amutan et al. (cited as reference 4 on the IDS filed 30 November 2006). The Office Action states:

> Claim 1 is drawn to a transposable element comprising at least four inverted repeats, forming at least two pairs of opposing pairs of inverted repeats, the element comprising DNA for insertion into a host genome, the DNA being located between two pairs of opposing repeats such that excision by a transposase or transposases of said pairs, in situ, is effective to be able to leave said DNA integrated into the host genome, without the presence of said repeats flanking said DNA insertion. Claim 6 specifies within claim 1 that the element has four inverted repeats. Claim 8 specifies within claim 1 that said pairs of homologous inverted repeats are heterologous to other pairs of inverted repeats. Claim 10 specifies that the transposable element of claim 1 comprises at least one genetic marker. Claim 19 specifies that the transposable element of claim 10 comprises at least one genetic marker associated with an identifiable step in the transposition/excision process. Claim 20 specifies within claim 19 that the marker is associated with the DNA for insertion into a host genome. Claim 22 specifies within claim 1 that the element is a class II transposable element. Claim 23 specifies within claim 1 that the transposase is encoded within the transposon. Claim 24 is drawn to a method for transforming an organism, comprising exposing replicative tissue of the organism to an element of claim 1 under conditions effective to incorporate the element into the genome thereof and, subsequently or simultaneously therewith, providing conditions suitable to excise a transposon said repeats from the genome, and selecting an organism, or tissue therefor, comprising the DNA intended for insertion lacking repeats in at least one orientation. Claim 25 specifies within claim 24 that the transformant organism is exposed to a source of active transposase. Claim 26 specifies within claim 25 that the source of active transposase comprises a helper plasmid or RNA encoding the transposase, or a transposase protein or integrated transposase source. Claim 32 specifies that the transposable element of claim 1 is effective to be able to leave said DNA integrated into the host genome without the presence of any transposon DNA.
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> Amutan et al. shows, e.g., at Figure 9, an element comprising two sets of inverted repeats, of two different transposons, with a small segment of DNA linking them. At the paragraph bridging pages 4 and 5, a method of using this element in a transposition process is taught. Upon excision of the two transposons, the small segment of DNA between them would remain in the chromosome.

This rejection is respectfully traversed. The Genencor publication WO 98/08960A does not disclose a functional transposon that is capable of transposition or excision because the "left" transposable Tan1 element is defective and is only capable of "launching" the Vader element contained within it. Thus, Genencor's Tan1 is not an element in which the

opposing repeats are "transposable by a transposase in situ," as required by the present claims.

In more detail, although Tan1 may appear initially to have two pairs of inverted repeats, these are surprisingly imperfect. Nevertheless, the key to understanding this element is to consider its biology, for instance how it was discovered, and its proposed use(s).

Tan1 was discovered by first finding Vader, realizing that it did not encode a transposase and then looking for the missing transposase. Tan1 appears always to include a copy of Vader, indeed it is defined that way by Genencor (e.g. Figures 8 and 9). If Tan1 did represent two separate elements (as required in the presently claimed invention), essentially a "left" Vader-like element that encoded the transposase and a "right" element that is Vader itself, one would expect to find the "left" Vader-like element separately.

However, there is no hint of this in Genencor. In fact, there is strong evidence to the contrary. In Example 6, Southern analysis was used to show that no such isolated (1.9kb) element exists in the genome of *A. niger* var *awamori*, from which Tan1 was isolated, and which contains multiple, and apparently highly mobile, copies of Vader.

Instead, the left element seems to be defective, but capable of "launching" the Vader element that it contains. The Applicants believe that the "left" Tan1 element is actually "borrowing" the right end of Vader to enable the whole Tan1 element to move.

Therefore, the "left" element is not a functional transposon capable of transposition or excision, as required in the present invention.

Furthermore, please note that Figure 9 illustrates one of the proposed uses for Tan1, its use as a "mutator" element, from which Vader will jump to insert in other areas of the genome. The point of the second part of Figure 9 is to illustrate the Vader element inserted into a new region of the genome, **not** to illustrate the deletion of the left-hand component of Tan1 (which, as discussed above, is incapable of such excision). This is clear from the text discussing Figure 9, and also from the lack of representation of the central domain in this second part.

In fact, excision of Vader from Tan1 would give a structure resembling one of our intermediates, with the "left" element and central domain only. However, as discussed above, there is no evidence that this can occur, only evidence that it cannot. Without being bound by theory, we believe that one or more of the sequence variations in the "inverted repeats" of Genencor leads the second repeat (from the left of the Tan1 element in Figures 8 and 9) to be non-functional, i.e., not suitable for the transposase. It is also possible that some difference in the adjacent sequence (5' or 3') causes the lack of function.

In any event, the Genencor system simply does not provide a transposable element in which the opposing repeats are "transposable by a transposase in situ". Thus, the claims are novel over Genecor.

The present application is also nonobvious over Genencor because it teaches towards a nonfunctional second pair of repeats and works in a different way than the present element/construct.

Furthermore, the "left" element of Genencor is actually required to leave the central nucleotides "naked" in the genome. That the authors of the Genencor patent had no such intention is immediately apparent from not only from a complete silence on the matter, but also from the fact that the authors did not even deem it necessary to determine the relevant nucleotides (represented by NNNNN in Figure 8D, second line). Therefore, Genencor **teaches away** from the present invention. Thus, the claims are nonobvious.

Claim 27, which was directed to a transformant organism, has been amended to only encompass the Class II elements. This requirement for a Class II element now distinguishes the organism from one produced by the prior art methods, such as homologous recombination.

The use of Class II elements provides insertions will be flanked by a short direct repeat. These repeats are characteristic of the insertion mechanism of the class II elements and their exact nature is characteristic of the specific element used. In the case of piggyBac the repeat is TTAA, so the final structure will be:

Flanking genomic DNA - TTAA - central domain - TTAA - flanking genomic DNA.

Other elements comprise other direct repeats. For example, mariner comprises TA, while for the *P* element it is 8 bases of variable sequence (but still a precise direct repeat of that sequence). Thus, the presence of this short repeat will be typical of an organism created by the present method, thus distinguishing it from organisms produced by prior art methods. Thus, the organisms of claim 27 are novel over the prior art and derive their nonobviousness from the use of the present construct.

Conclusion

It is submitted that this case is in condition for allowance, and passage to issuance is respectfully requested. It is believed a one-month Extension of Time is required, and a Request for Extension of Time together with the appropriate fee is submitted via the Electronic Filing System with this Response. If this is incorrect, please deduct the correct fee, and any fee required for any further extension of time needed, from deposit account 07-1969.

Respectfully submitted,

/ellenwinner/

Ellen P. Winner
Reg. No. 28,547

Greenlee, Winner and Sullivan, P.C.
4875 Pearl East Circle, Suite 200
Boulder, CO 80301
Telephone: (303) 499-8080
Facsimile: (303) 499-8089
E-mail: usptomail@greenwin.com
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